

### **REMARKS**

Applicants have considered the office action mailed January 24, 2006 in connection with the above-identified patent application.

#### **Statement of Substance of Interview**

Applicants' representative, the undersigned, thanks Examiner Sines and Supervisory Examiner Gakh for courtesies extended during an in-person interview at the U.S. Patent and Trademark Office on March 28, 2006. Also in attendance were Applicants' representative, Mary Ann Dillahunty, and Kalyan Handique, Ph.D., Chief Technical Officer of HandyLab, Inc., (the assignee of the instant application).

During that interview, the patentability of the then-pending claims over the cited references was discussed. No agreement was reached however regarding the patentability of the then-pending claims. Applicants undertook to consider further claim amendments in conjunction with filing a RCE.

#### **Amendments to Specification and Drawings**

With the instant amendment and response, Applicants amend the specification and drawings to correct various typographical errors and other various clerical errors, the nature of which would be clear to one of ordinary skill in the art and which are, as follows.

FIG. 1 is amended to delete reference numeral 134. Applicants respectfully point out that, as would be clear from the accompanying portion of the specification, the correct reference numeral 134 refers to a different element, as shown in FIG. 2.

FIGs. 2, 4, 8a, and 9a are amended to insert references to corresponding figures wherein arrows are shown to indicate a cross sectional view.

FIG. 4 has been amended to insert (or correct position of) various reference numerals, including 156, 410, 420, 901, 915, 950, 972, 973, 979, and 981. The positioning of such new or revised reference numerals is based on other drawings as filed and the accompanying description found in the specification as filed.

FIGs. 8a and 8b have been amended to insert reference numeral 820, as found in the accompanying description in the specification as filed.

FIGs. 9a and 9b have been amended to insert reference numeral 822, as found in the accompanying description in the specification as filed.

FIGs. 11a – 11c have been amended to insert reference numeral 526, and FIG. 11b has been amended to insert reference numeral 504, as found in the accompanying description in the specification as filed.

FIGs. 12a and 12b have been amended to insert various reference numerals, including 200, 206, 212, 214, 915, and 950. The positioning of such reference numerals is based on other drawings as filed and the accompanying description found in the specification as filed.

FIG. 15c has been amended to insert various reference numerals, including 654, 656, 658, 660, and 682. The positioning of such reference numerals is based on other drawings as filed (in particular FIGs. 15a and 15b) and the accompanying description found in the specification as filed.

All of the amendments to the figures are therefore merely for completeness and consistency, and no new matter is introduced thereby.

In respect of the amendments to the specification, paragraphs on pages 6, 7, 10, 13, 14, 19, 20, 21, 22 and 24 have been amended to correct various errors of spelling, grammar, or in reference to Figure numbers.

Paragraphs at pages 8, 9, 13, 16, 20, 21, and 23 have been amended to correct terminology and reference numerals in the figures where inconsistent with other usage within the specification as filed and where it would be clear which element is correct, or to insert description of reference numerals from the figures where such description would be clear to one of ordinary skill in the art.

Additionally, the filing date in the reference to application serial no. 09/953,921 in the paragraph at page 9, line 5, has been corrected.

Regarding the paragraph beginning at page 21, line 14, Applicants have also expanded the acronym “TRS” to “thermally responsive substance”. This expansion can be found throughout U.S. patent application serial no. 09/953,921 (now U.S. Patent No. 6,575,188) — for example in the Abstract, Summary of Invention, and claims — to which the instant application claims priority. Since the specification of application serial no. 09/953,921 is incorporated by reference into the specification of the instant application, this amendment introduces no new matter.

Accordingly, none of the foregoing amendments to the specification and claims introduces new matter and entry thereof is respectfully requested.

### **Amendments to the Claims**

Prior to entry of the instant amendment, claims 1-4, 9, 12 – 14, 16 – 19, 21 – 23, 25 – 30, 32, 33 and 35 – 44 are pending in the application, and claim 38 is withdrawn from consideration.

With the instant amendment, Applicants amend claims 1, 3, 4, 12 – 14, 16, 18, 19, 21 – 23, 25 – 30, 32, 33, 35 – 37, and 39 – 44, and cancel claims 17 and 38. New claims 45 – 51 are also introduced herein.

Support for the new and amended claims contained herein are found in the specification as filed, as follows.

Claims 1 and 12, as amended herein, are supported by, for example, FIG. 12, and accompanying text of the specification at, for example, pages 14 – 15.

Claims 4, 19 and 21 are amended herein to recite a “lysed microdroplet”, a term which is found in the specification as filed at, for example, page 15, line 9.

In claims 1, 12, and 13, the term “vent” is changed to “vented positioning element” (see, *e.g.*, specification as filed at page 14, line 19).

Limitations recited in amended claims 13 and 14 can be found in the specification as filed at, *e.g.*, pages 21 – 22.

Claims 16 and 40, as amended herein, are supported by, for example, FIGs. 13a and 13b, and accompanying text of the specification at, for example, page 16.

The term “cell-containing sample” as introduced into claims 25 and 26 herein find support in the specification as filed at, *e.g.*, page 2, line 17.

In claims 1, 2, 16, 18, 22, 33, 35, 37, 39, 40, and 41, the term “lysing zone” is changed to “lysing module”, as found at least at page 14, line 22 of the specification as filed.

Additionally, claims 1, 3, 4, 14, 16, 18, 21, 23, 24, 25, and 26, are rewritten from active to passive language.

Furthermore, claims 3, 4, 21, 27, 28, 29, 30, 32, 33, 35, 36, 37, 39, and 44 are rewritten to more particularly recite what is considered to be the invention, and the dependencies of claims 3, 4, 18, 22, 25, 26, 41, 42, and 43, are also amended to ensure consistency with the other amendments described herein.

Finally, support for new claims 45 – 51, is as follows:

Claims 45 and 46: at, for example, page 15, lines 3 – 5, and page 16, line 5.

Claims 47 and 48: at least at page 11, line 18, to line 20.

Claims 49 and 50: at least at page 21, lines 17 – 18.

Claim 51: at least at page 9, lines 11 – 12.

Accordingly, the new claims presented herein are supported by the specification as filed, and thereby introduce no new matter. Entry thereof is respectfully requested.

### **Elections/Restrictions**

The Examiner has requested cancellation of claim 38, which is withdrawn from prosecution as drawn to a non-elected invention. With the instant amendment, Applicants herewith cancel claim 38 without prejudice. Applicants reserve the right to prosecute the subject matter of claim 38 in one or more continuation or divisional applications.

Applicants also note that in the Office Action dated January 11, 2005, the Examiner withdrew claims 39 – 44 for supposedly not being drawn to an elected invention, and requested that Applicants cancel such claims. However, in subsequent prosecution, claims 39 – 44 were never designated as “withdrawn” or “cancelled” by Applicants, and the claims remained under examination, and in fact currently stand rejected. Applicants assume that the continued examination of these claims means that the Office does not actually consider them to have been withdrawn.

Furthermore, with the instant amendment, claims 39 – 44 have been amended as follows: claim 39 (formerly an independent claim) has been amended to depend from claim 1, a previously elected claim; claim 40 has been amended to recite limitations present in the remaining claims under examination; and claims 41 – 45 have been amended to depend from claim 33, also a previously elected claim. Applicants therefore believe that claims 39 – 44 as amended herein should not be withdrawn and are properly examined with the remainder of the instant claims. Applicants request the Examiner’s acknowledgment to this effect in his next official action or in conjunction with a Notice of Allowability.

### **REJECTIONS OF THE CLAIMS**

The Examiner has rejected claims 1 – 4, 9, 12 – 14, 16 – 19, 21 – 23, 25 – 30, 32, 33, 35 – 37, and 39 – 44, under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent Application Publication No. 2002/0055167 to Pourahmadi, (“Pourahmadi”, hereinafter), in view of U.S. Patent No. 6,130,098 to Handique (“Handique” hereinafter). After entry of the

instant amendments, claim 17 is cancelled. Accordingly, the claims which stand rejected are claims 1 – 4, 9, 12 – 14, 16, 18, 19, 21 – 23, 25 – 30, 32, 33, 35 – 37, and 39 – 44.

The U.S. Patent and Trademark Office (“PTO”) bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, the PTO must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings in the manner suggested by the PTO. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Second, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would be successful. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in the Applicant’s disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established. Applicants respectfully submit that the Examiner has not satisfied the Office’s burden of establishing a *prima facie* case.

In essence, the Examiner has alleged, in the Office Action mailed January 24, 2006, that one of ordinary skill in the art would have had a reasonable expectation that an actuator and vent taught by Handique could be successfully combined with a microfluidic cartridge of Pourahmadi. Applicants respectfully submit that this rejection is rendered moot by the claim amendments presented herein.

Applicants’ instant claim 1, as amended herein, recites a microfluidic device comprising a lysing module configured to receive a microdroplet and having a lysing mechanism, an actuator, and a vented positioning element. Applicants instant claim 16, as amended herein, recites a microfluidic device comprising a lysing module configured to receive a microdroplet and having a lysing mechanism, a first gas actuator, a positioning element, and a second gas actuator. Applicants’ instant claims 27, 33, and 40, as amended herein, recite methods of lysing cells contained in microdroplets.

In particular, Applicants point out that the microfluidic devices and methods of Applicants' claims, as amended herein, recite manipulations of microdroplets of fluid. Furthermore, the disposition of the various elements, such as the actuator, the vented positioning element, the second actuator, and the positioning element, relative to one another is such that, in Applicants' claimed invention, a cell-containing microdroplet of sample is positioned, and the cells lysed.

Pourahmadi teaches a continuous-flow microfluidic cartridge having a collection of components suitable for manipulation of fluids, including lysing of samples, under continuous flow (see, *e.g.*, Pourahmadi at ¶ [0017]). In general, Pourahmadi does not specify the components recited in Applicants' claims and in the recited locations and configurations.

Thus, although Pourahmadi refers generally to the use of "fluid motive sources" to move fluid through the cartridge (Pourahmadi, at paragraphs [0065] to [0067]), none of these sources is shown in any specific configuration with respect to, *e.g.*, a lysing chamber. In particular, Pourahmadi provides no specific teaching of a location of a fluid motive source, such as a "pneumatic pressure source," when "located inside the cartridge," but instead merely states that, when *outside*, "the cartridge has suitable ports, vents, or channels for interfacing with the source" (Pourahmadi, at paragraph [0067]). This disclosure is not specific enough to lead one of ordinary skill in the art to Applicants' claimed configuration(s), either alone or in combination with Handique, as further discussed hereinbelow. For example, Pourahmadi does not teach a pair of gas actuators configured to move a microdroplet into a lysing position and to move a microdroplet downstream from a lysing position, as recited in claim 16, as amended herein.

The deficiencies of Pourahmadi are not provided by Handique, which teaches a combination of an actuator and a vent for creating and moving a microdroplet of fluid. For example, regarding claim 1, reciting a microfluidic device, nothing in the teachings of Handique suggests that a combination of a vent and an actuator would be used to position a microdroplet in a lysing position. Regarding claim 16, also reciting a microfluidic device, nothing in Handique suggests using a second actuator to create a microdroplet from fluid present in a lysing position.

Thus at least claims 1, 16, and those depending therefrom, are not obvious over a combination of Pourahmadi and Handique for at least the foregoing reasons.

The Examiner has alleged that “it would have been obvious to a person of ordinary skill in the art to incorporate [such] a thermopneumatic fluid transport system with a microfluidic apparatus for facilitating effective sample fluid transport.” Applicants respectfully disagree.

Since Pourahmadi discloses a continuous-flow type microfluidic device (see, *e.g.*, Pourahmadi at ¶ [0017]), and not one that manipulates microdroplets as required by the instant claims, and, by contrast, Handique discloses a microfluidic device for manipulating microdroplets, one of ordinary skill in the art would not have been motivated to combine the teachings of Handique with those of Pourahmadi. Furthermore, Handique does not teach lysing cells in a microdroplet. Thus, one in possession of the teachings of Handique would not have been motivated to consider the teachings of Pourahmadi.

Accordingly, at least instant claims 27, 33, and 40, reciting methods, and claims depending therefrom, are not obvious over a combination of Pourahmadi and Handique.

Accordingly, neither Pourahmadi nor Handique, alone or in combination teaches or discloses a microfluidic device having the components disposed in the configurations recited in the instant claims. Therefore, for at least the foregoing reasons, Applicants’ claims are not obvious over the combination of Pourahmadi and Handique.

Dependent claims are nonobvious under 35 U.S.C. § 103 “if the independent claims from which they depend are nonobvious.” *In re Fine* 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03. Claims 3, 7, 8, 14 – 16, 18, and new claims 38 – 51 depend directly or indirectly from claim 1, and claims 20, 21, 24 – 26, 28, 30 – 33, and new claims 52 – 56 depend directly or indirectly from claim 19. Therefore, none of these claims is obvious over Pourahmadi in combination with Handique.

Accordingly and in conclusion, Applicants respectfully submit that all of the pending claims, whether previously rejected under 35 U.S.C. § 103 or whether introduced herein, are non-obvious in view of a combination of Pourahmadi and Handique, and ask that the rejection of record be removed.

### **CONCLUSION**

In view of the above remarks, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner’s rejections and early notification to this effect are earnestly solicited. If, in the opinion of the

Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 839-5070.

No fee is believed owed in connection with filing of this amendment and response. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. No. 19662-029001) for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: June 26, 2006

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**IN THE DRAWINGS**

*Marked-up versions of FIGs. 1, 2, 4, 8a, 8b, 9a, 9c, 11a – 11c, 12a, 12b, and 15c showing changes in red, follow this page; replacement sheets are positioned at the end of this amendment and response.*



METHODS AND SYSTEMS FOR RELEASING INTRACELLULAR MATERIAL  
FROM CELLS WITHIN MICROFLUIDIC SAMPLES OF FLUIDS

Betty Wu et al.  
10/014,519 / 19662-029001  
ANNOTATED SHEET

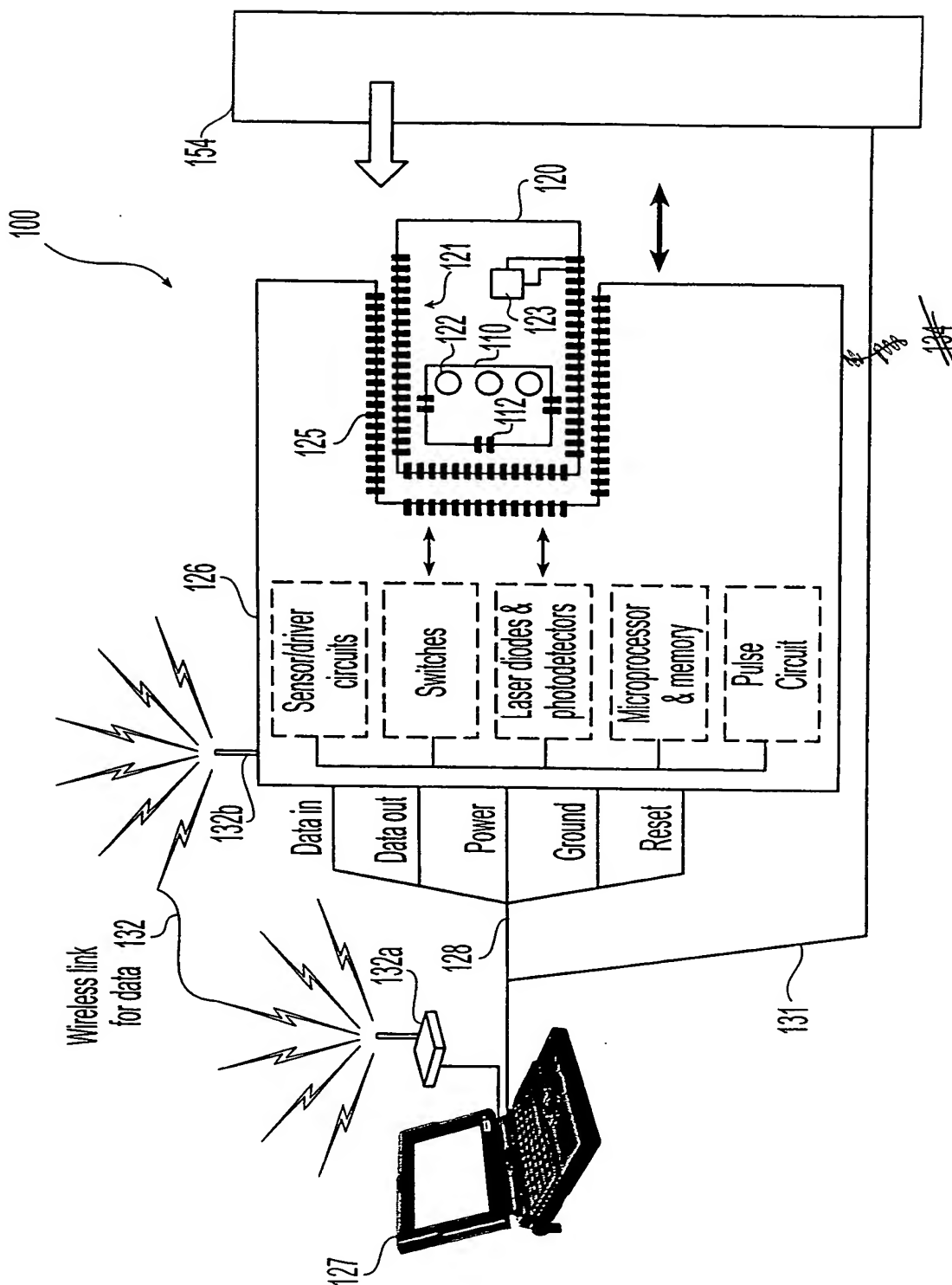


Fig. 1



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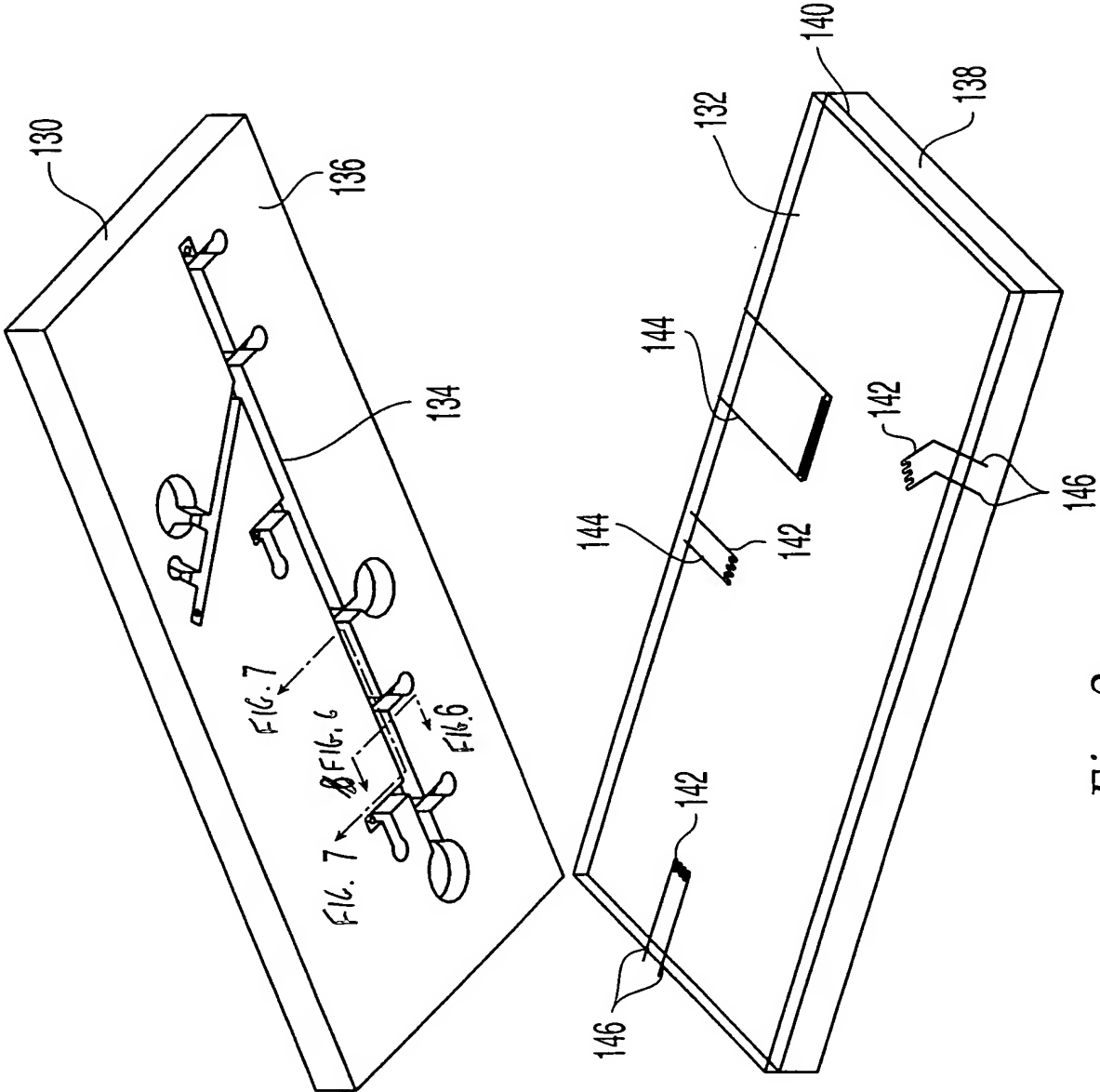


Fig. 2



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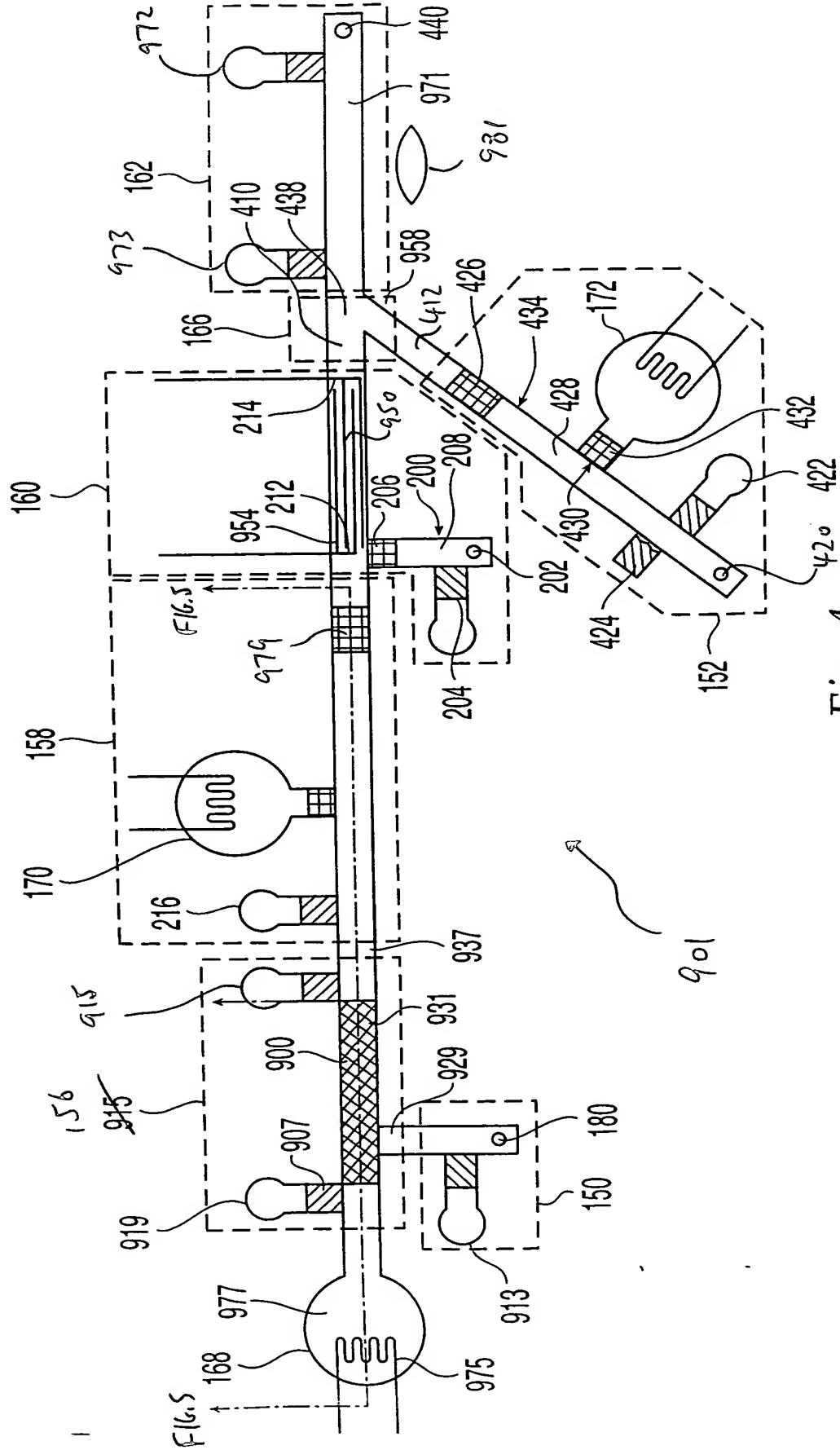
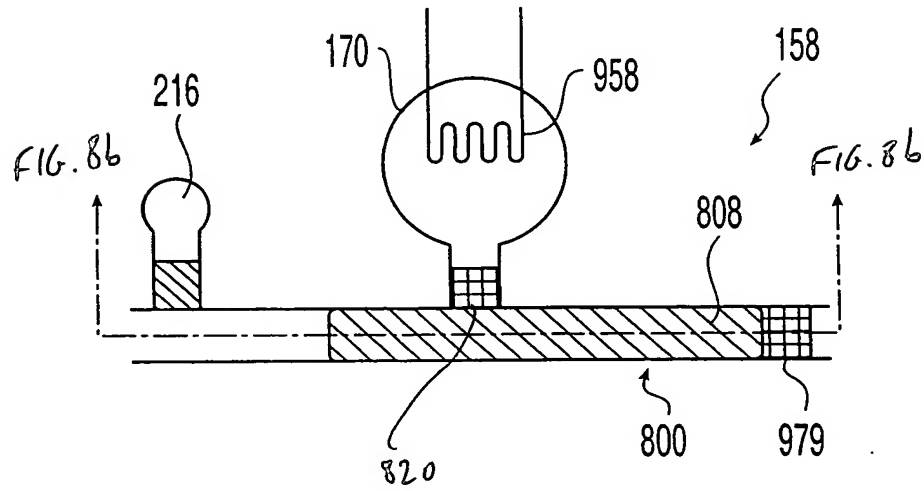


Fig. 4

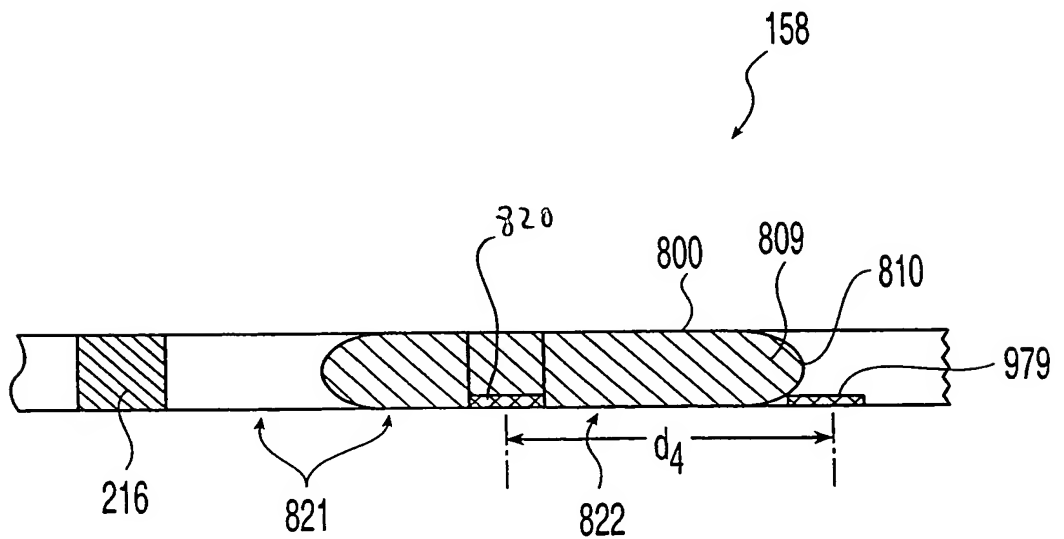


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*Fig. 8a*



*Fig. 8b*



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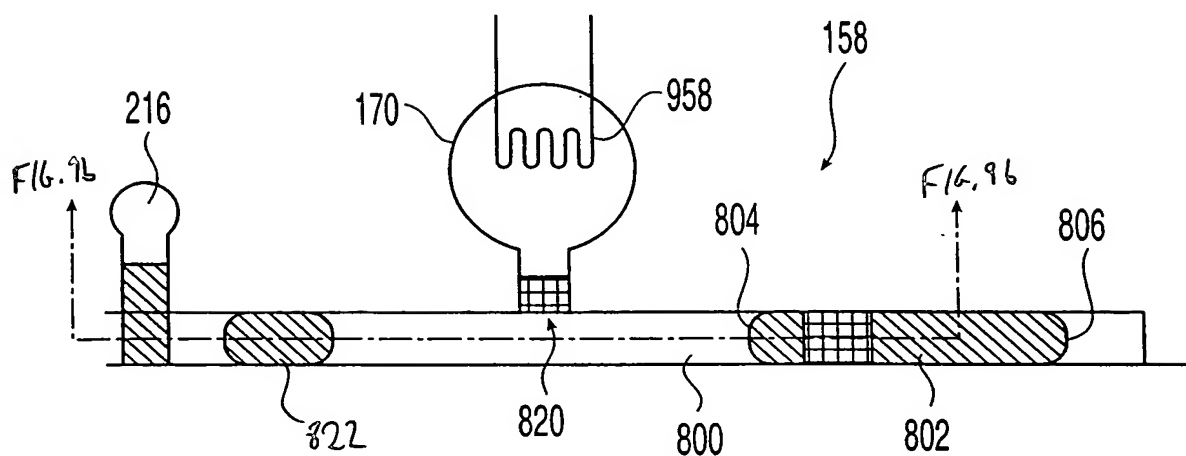


Fig. 9a

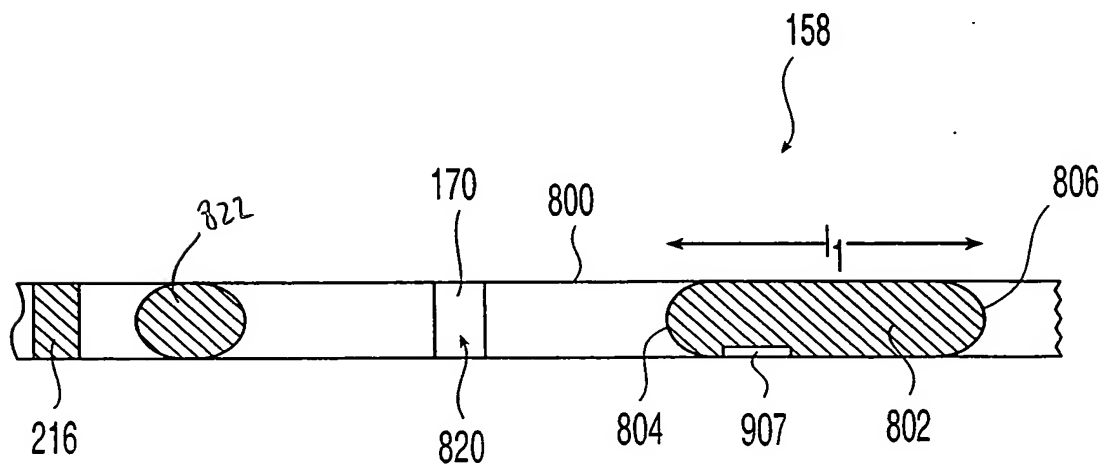


Fig. 9b



METHODS AND SYSTEMS FOR RELEASING INTRACELLULAR MATERIAL  
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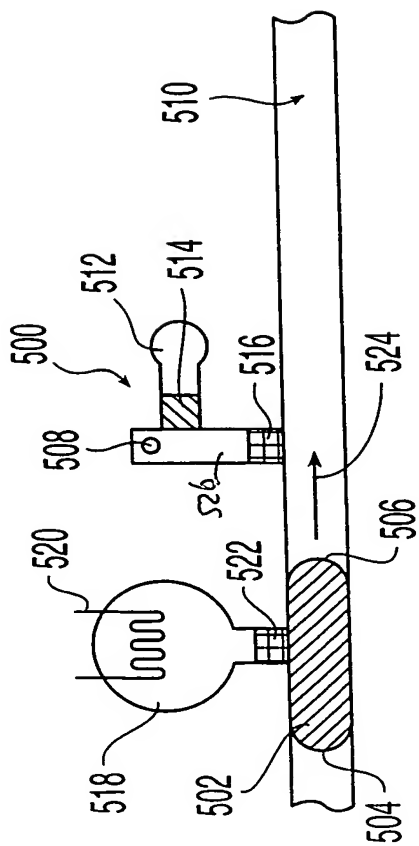


Fig. 11a

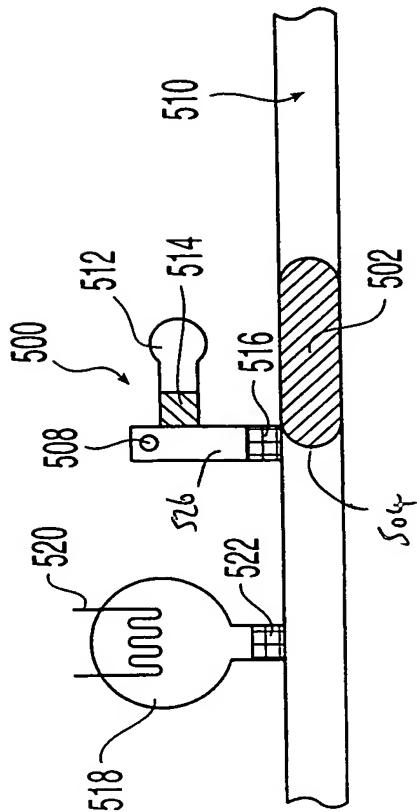


Fig. 11b

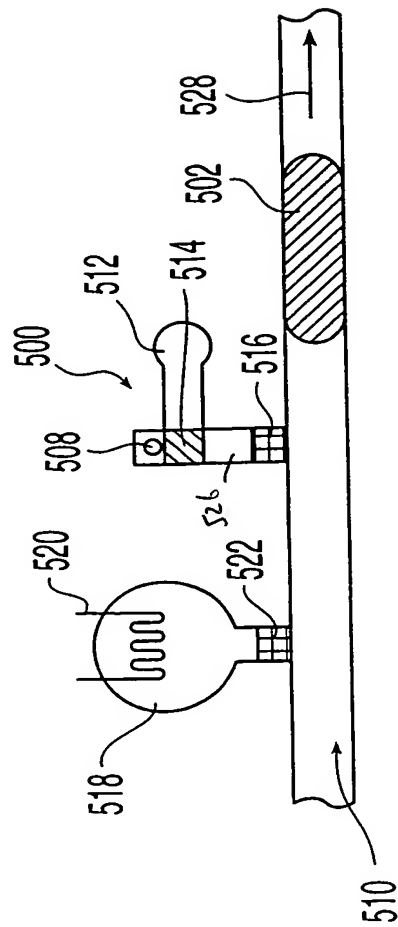


Fig. 11c

Fig. 12a

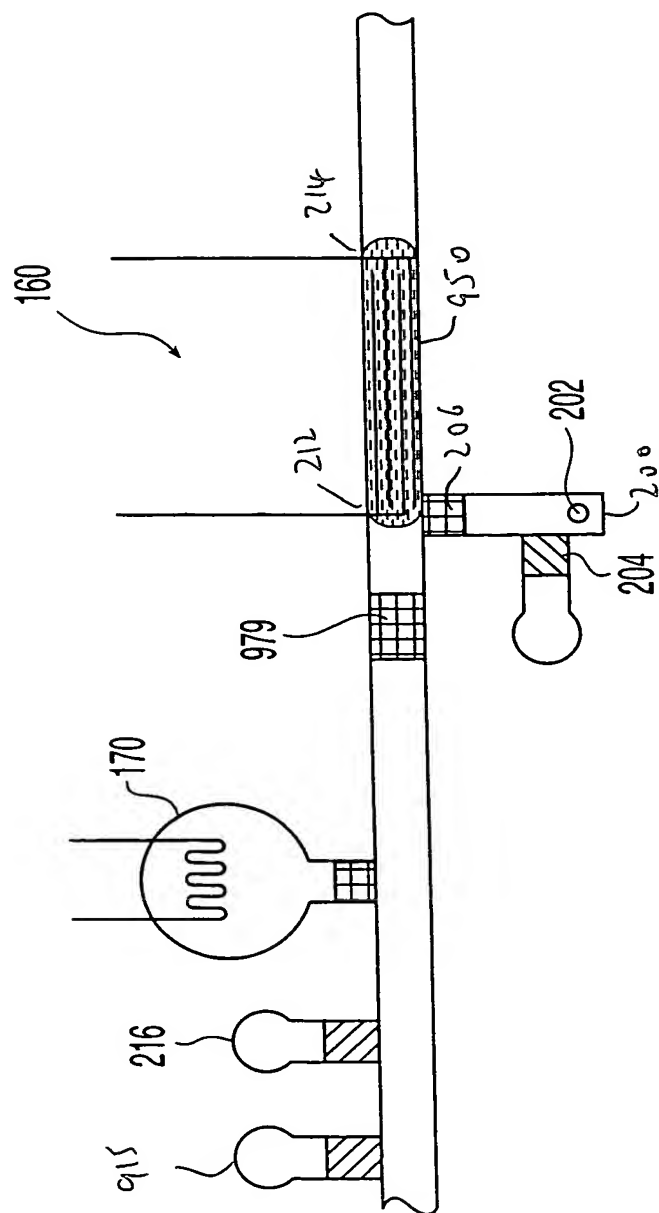
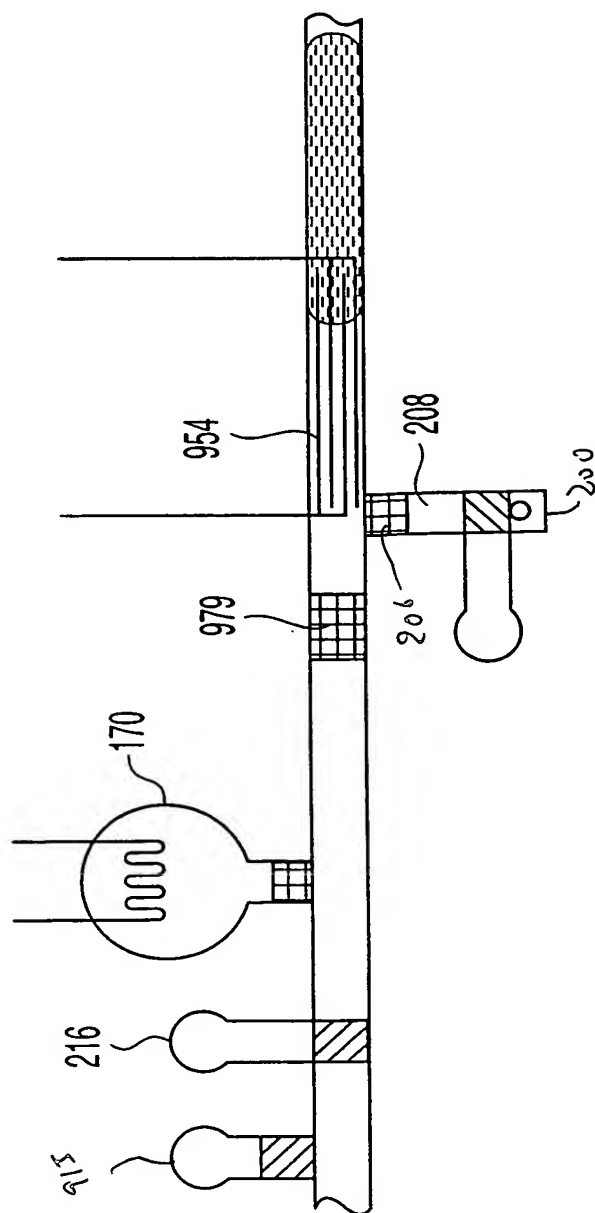


Fig. 12b





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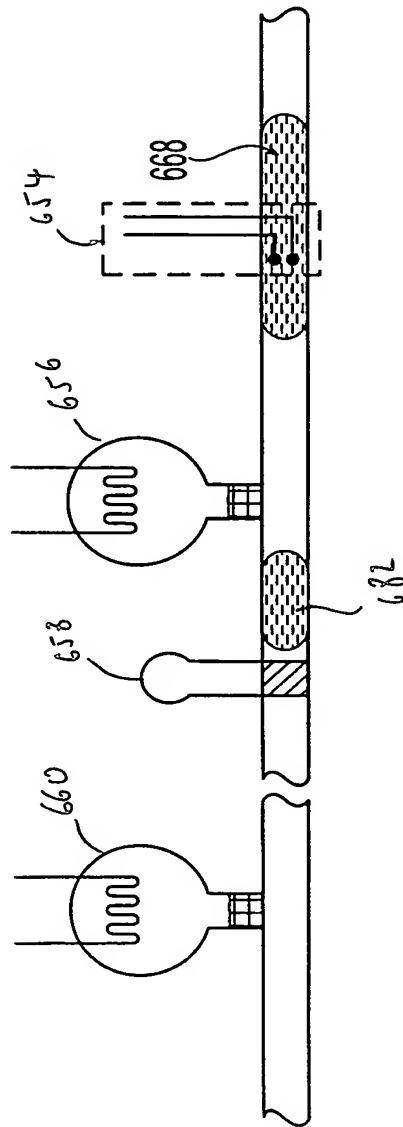


Fig. 15c